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REVIEW

SPECIAL ISSUE
THE INTEGRATIVE BIOLOGY OF THE HEART

Effects of hemodynamic load on cardiac remodeling in fish and mammals: the value of comparative models

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ABSTRACT

The ability of the vertebrate heart to remodel enables the cardiac phenotype to be responsive to changes in physiological conditions and aerobic demand. Examples include exercise-induced cardiac hypertrophy, and the significant remodeling of the trout heart during thermal acclimation. Such changes are thought to occur in response to a change in hemodynamic load (i.e. the forces that the heart must work against to circulate blood). Variations in hemodynamic load are caused by either a volume overload (high volume of blood returning to the heart, impairing contraction) or a pressure overload (elevated afterload pressure that the heart must contract against). The changes observed in the heart during remodeling are regulated by multiple cellular signaling pathways. The cardiac response to these regulatory mechanisms occurs across levels of biological organization, affecting cardiac morphology, tissue composition and contractile function. Importantly, prolonged exposure to pressure overload can cause a physiological response – that improves function – to transition to a pathological response that causes loss of function. This Review explores the role of changes in hemodynamic load in regulating the remodeling response, and considers the cellular signals responsible for regulating remodeling, incorporating knowledge gained from studying biomedical models and comparative animal models. We specifically focus on the renin–angiotensin system, and the role of nitric oxide, oxygen free radicals and transforming growth factor beta. Through this approach, we highlight the strong conservation of the regulatory pathways of cardiac remodeling, and the specific conditions within endotherms that may be conducive to the development of pathological phenotypes.

KEY WORDS: Renin–angiotensin system, Ventricular hypertrophy, Physiological cardiac remodeling, Pathological cardiac remodeling, Pressure overload, Volume overload

Introduction

An increase in hemodynamic load (see Glossary) can initiate significant changes to the vertebrate heart that lead to modifications in its structure and function. Depending on the cause of the change in hemodynamic load, these changes can be beneficial (improving function) or detrimental, referred to as physiological or pathological remodeling, respectively. Cardiac remodeling, including that caused by a change in hemodynamic load, has been described in multiple vertebrate species in response to a variety of physiological challenges, and recent studies have begun to disentangle the cellular pathways responsible for the different morphological and functional phenotypes. The purpose of this Review is to investigate the signaling pathways that regulate the remodeling response, integrating what is known from studying mammalian biomedical models with work using more comparative models. We first discuss the responses of the mammalian heart to increases in hemodynamic load and how these can result in pathological conditions. We then compare the mammalian responses with those of comparative models responding to changes in hemodynamic load caused by changes in environmental conditions, such as low-temperature acclimation. To introduce the mechanisms that regulate these responses, we then focus on the renin–angiotensin system, as well as the role of nitric oxide (NO), reactive oxygen species (ROS; see Glossary) and transforming growth factor beta (TGF-β), investigating how their roles change as a physiological response transitions into a pathological response. Integrating knowledge gained from studying comparative and biomedical models shows us how cellular processes that evolved to enable cardiac plasticity during physiological challenges are also responsible for driving pathological changes to the heart. We end this work by considering the environmental stressors that could lead to cardiac pathologies in wild populations.

Physiological and pathological responses to an increase in hemodynamic load

The hemodynamic load on the heart is primarily determined by the rate of blood flow and the pressure that it is under. In a closed circulatory system, these are regulated by multiple factors. Blood flow is regulated by heart rate and stroke volume, whereas factors that regulate blood pressure include vascular resistance, volume of circulating blood, elasticity of vessel walls, blood viscosity and the contractile force of the heart. A change in any of these factors, without compensation, results in a change in hemodynamic load. Acutely, an increase in hemodynamic load caused by a volume overload increases cardiac output through the Frank–Starling response (see Glossary). The release of catecholamines at the start of exercise also activates β-adrenergic receptors, leading to an increase in Ca^{2+} cycling during activation. Together, these mechanisms cause an increase in cardiac output.

Cardiac remodeling in response to prolonged exercise is caused by changes in gene expression and is initiated when mechanosensitive elements in the cell membrane and sarcomere are activated, leading to the stimulation of cell signaling cascades. An increase in the stretch of the myocardium leads to the stimulation of mechanically sensitive tyrosine kinase receptors and ion channels in the cell membranes that activate the p38–JNK–ERK mitogen-activated protein kinase (MAPK) cascade (Husse et al., 2007; Reed et al., 2014). Increased stretch of the sarcomere also activates ERK (Sheikh, et al., 2008) and p38 (Okamoto, et al., 2013; Wong et al., 2012) pathways through increased interaction of the N2B element of titin with the four-and-a-half LIM domains 1 and 2 (FHL1 and

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Glossary

Cardiac hypertrophy
An increase in heart size owing to either increased cell size (cellular hypertrophy) or cell number (hyperplasia).
Compact myocardium
The outer layer of fish myocardium characterized by tightly packed and circumferentially arranged myocytes. This muscle layer encases the spongy myocardium.
Concentric ventricular hypertrophy
A condition where changes in heart morphology result in a relative increase in ventricle wall thickness, but a decrease in the chamber volume.
Eccentric ventricular hypertrophy
A condition where changes in heart morphology result in a relative increase in ventricle wall thickness and chamber volume.
Ejection fraction
The percentage of blood that leaves the heart when it contracts.
Frank–Starling response
A mechanism by which the heart adjusts cardiac output to venous return. An increase in preload increases chamber volume, stretching the myocardium and increasing the sarcomere length of the myocytes; this increases the number of cross-bridges and the Ca^{2+} sensitivity of force generation.
Hemodynamic load
The force that the heart works against to circulate blood through the cardiovascular system. This is determined in part by blood pressure, blood viscosity and the resistance to flow generated by the capillary beds and other blood vessels.
Mitochondrial permeability transition pore
A non-specific pore in the inner mitochondrial membrane that enables passage of molecules of <1.5 kDa, including protons. This pore opens during mitochondrial calcium overload, especially if accompanied by oxidative stress, elevated phosphate concentrations and adenine nucleotide depletion.
Pressure overload
A condition in which the heart is contracting against an excessive afterload during systole.
Reactive oxygen species
Highly reactive molecules that can act as signaling molecules turning cellular pathways on or off, but are damaging to cellular components at higher concentrations. These include hydrogen peroxide (H_2O_2), superoxide ($O_2^{\bullet-}$), hydroxyl radical ($OH^{\bullet}$) and singlet oxygen ($^1O_2$).
Renin–angiotensin system
A hormonal system that regulates blood pressure, blood volume and vascular resistance.
Spongy myocardium
The inner layer of fish myocardium characterized by a fine arrangement of muscular trabeculae that span the heart's chamber.
Ventricle dilation
An increase in the volume of the ventricle chamber with a concurrent decrease in the thickness of the ventricle wall.
Volume overload
A condition that is initiated when too great a volume of blood returns to a chamber of the heart for it to contract properly.

List of symbols and abbreviations

ACE	ANG-converting enzyme
Akt	protein kinase B
ANG	angiotensin
ARA	arachidonic acid
AT	angiotensin type
BK	bradykinin
CK	cytokine
CMS	chronic mountain sickness
DAG	diacylglycerol
ERK	extracellular signal-regulated kinase
ETC	electron transport chain
G	G protein or guanine nucleotide-binding protein
GRK2	G-coupled receptor kinase 2
H_2O_2	hydrogen peroxide
IKK	IκB kinase
IL	interleukin
IP_3	inositol trisphosphate
JNK	c-Jun N-terminal kinase
LV	left ventricular
MAPK	mitogen-activated protein kinase
mTOR	mechanistic target of rapamycin
NFAT	nuclear factor of activated T-cell
NF-κB	nuclear factor kappa B
NO	nitric oxide
NOS	nitric oxide synthase
NOS1	neural tissue-derived NOS
NOS2	cardiomyocyte-derived NOS
NOS3	endothelial nitric oxide synthase
NOX	NADPH oxidase
$\bullet O_2$	reactive oxygen species
$O_2^{\bullet-}$	superoxide
$^1O_2$	singlet oxygen
$OH^{\bullet}$	hydroxyl radical
PGC-1α	peroxisome proliferator-activated receptor-γ coactivator-1 protein α
PLA2	phospholipase 2
PLC	phospholipase C
ROS	reactive oxygen species
RV	right ventricular
RyR2	ryanodine receptor 2
SERCA2a	sarco(endo)plasmic reticulum Ca^{2+} ATPase 2a
SR	sarcoplasmic reticulum
TGF-β	transforming growth factor-β
TNF	tumor necrosis factor
TNFR1	TNF receptor-1
TNFα	tumor necrosis factor α
β-AR	β-adrenergic receptor

FHL2) proteins (Strom et al., 2024). These mechanically activated pathways are linked to pathological remodeling in mammals (Chiquet et al., 2009; Strom et al., 2024), and are also stretch activated in rainbow trout (*Oncorhynchus mykiss*) cardiac fibroblasts (Johnston and Gillis, 2020).

In mammalian species, exercise training can result in physiological cardiac remodeling that leads to functional and morphological changes to the heart (Oldfield et al., 2020; Nakamura and Sadoshima, 2018). These can include a reduction in diastolic and systolic pressures as well as an increase in left ventricular ejection fraction (see Glossary; Oldfield et al., 2020). However, not all training affects the heart equally, and differences in how the heart's structure is remodelled are dependent, in part, on the type of training (Dorn, 2007) (Fig. 1, Table 1). For example, aerobic training that involves the use of a large muscle mass (e.g. long-distance running) results in volume overload (see Glossary) that can initiate eccentric ventricular hypertrophy (see Glossary), where there is an increase in heart size, proportional increases in left ventricle (LV) wall thickness and chamber volume, a proportional increase in the density of capillaries in the tissue and a potential decrease in collagen content (Fernandes et al., 2015) (Table 1). Eccentric hypertrophy is due, in part, to hypertrophy of the cardiac myocytes through the addition of sarcomeres in series, resulting in an increase in cell length (Fernandes et al., 2011; Nakamura and Sadoshima, 2018). Comparatively, resistance training, which involves short, intense contractions of a small muscle mass (such as weightlifting), can lead to a pressure overload (see

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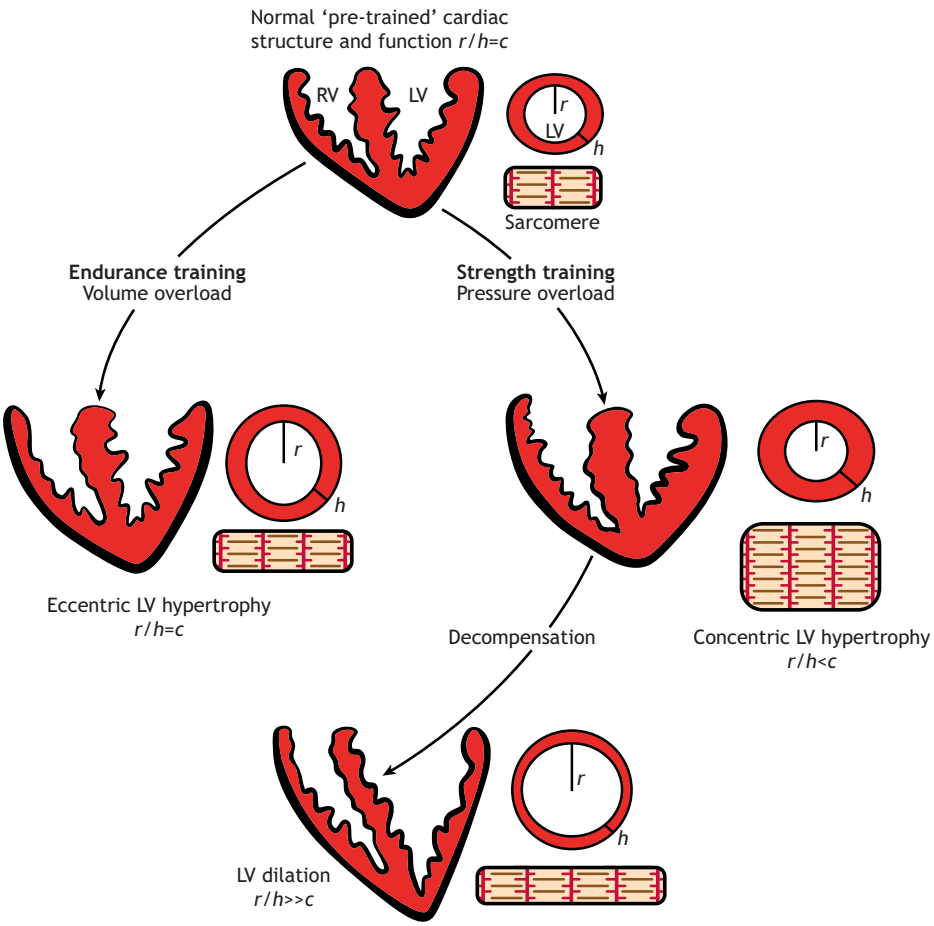

Fig. 1. A summary of the changes to the mammalian heart during eccentric left ventricle (LV) hypertrophy, concentric LV hypertrophy and dilated LV hypertrophy. Wall stress (*c*) at equal pressures is proportional to the ratio of internal ventricular radius at end diastole (*r*) and ventricle wall thickness (*h*).

Glossary) caused by increased vascular resistance. This leads to the development of concentric ventricular hypertrophy (see Glossary), where there is an increase in LV wall thickness and a decrease, or no change, in the volume of the LV chamber (Grossman et al., 1975) (Table 1). The cellular hypertrophy seen in concentric hypertrophy is caused by the addition of sarcomeres in parallel (Fernandes et al., 2011; Nakamura and Sadoshima, 2018).

Importantly, physiological remodeling of the heart caused by either pressure or volume overload can reverse upon cessation of the exercise stimulus (Nakamura and Sadoshima, 2018). However, concentric hypertrophy can transition to a pathological phenotype with sustained exercise over time, a phenomenon called 'decompensation', resulting in left ventricle dilation (see Glossary and Fig. 1, Table 1). This transition is thought to be initiated by a chronic increase in ventricular pressure caused by the associated high vascular resistance (Grossman et al., 1975). It has also been suggested that the transition to a pathological phenotype is due to an imbalance between exercise intensity and rest, with insufficient recovery leading to hypertrophy and fibrosis (Heidbuchel et al., 2012). Pathological right ventricle (RV) hypertrophy can also occur in otherwise healthy humans with prolonged exposure to high altitude. This syndrome, called chronic mountain sickness (CMS), is caused by pulmonary hypertension owing to an increase in blood viscosity resulting from comparatively high hematocrit (León-Velarde et al., 2005; Villafuerte and Corante, 2016). However, CMS can abate upon return to lower altitude, indicating that the changes to the heart are reversible (León-Velarde et al., 2005; Villafuerte and Corante, 2016). For more discussion regarding pathological and physiological cardiac hypertrophy, please see Oldfield et al. (2020) and Gibb and Hill (2018).

Cardiac remodeling in comparative models

Cardiac remodeling in comparative models has been found to occur in response to a variety of physiological challenges. For example,

Table 1. Comparison of the structural, compositional and functional changes of the left ventricle (LV) in the mammalian heart during eccentric LV hypertrophy, concentric LV hypertrophy and LV dilation

	Eccentric LV hypertrophy	Concentric LV hypertrophy	LV dilation
Size of left ventricle	↑	↑ or ≅	↑
Changes to left ventricle chamber and wall	↑ in LV wall thickness proportional to ↑ in chamber volume	↑ in LV wall thickness without proportional ↑ in chamber volume	↓ in LV wall thickness
Myocyte morphology	↑ in length due to addition of sarcomeres in series	↑ in width due to addition of sarcomeres in parallel	↑ in length due to addition of sarcomeres in series
Cardiac function	↑↑ or ≅	≅	↓ in systolic function
Capillary density	↑	↑	↓
Relative collagen content	≅	≅	↑

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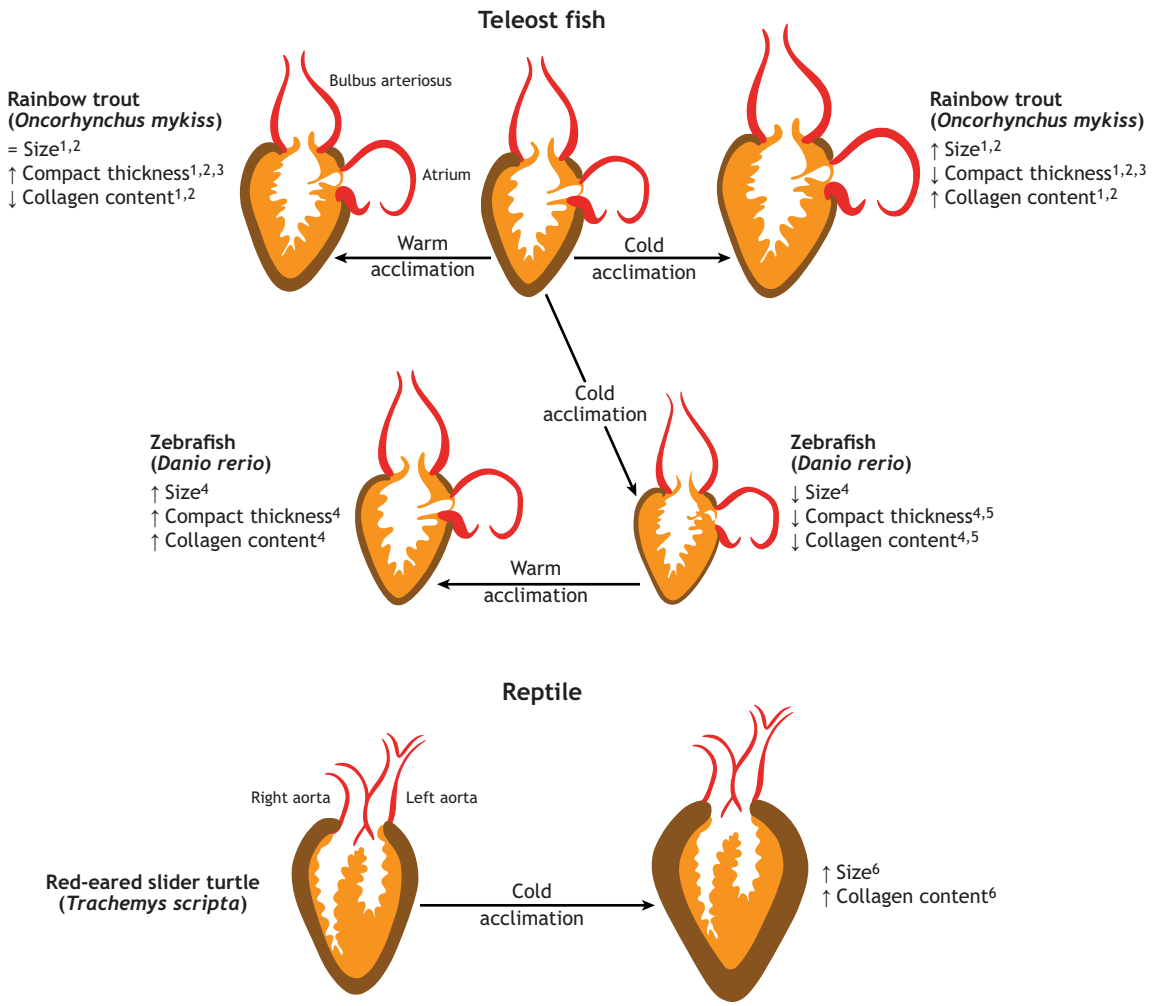

Fig. 2. The effect of thermal acclimation on the morphology and composition of hearts in two teleost fish and a reptile. Rainbow trout (*Oncorhyncus mykiss*), zebrafish (*Danio rerio*) and red-eared slider turtle (*Trachemys scripta*). Compact thickness is shown in brown, bulbous arteriosus, atrium and aorta are shown in red and spongy myocardium is shown in orange; collagen content is not shown. [1]Klaiman et al. (2011); [2]Keen et al. (2016a); [3]Klaiman et al. (2014); [4]Shaftoe et al. (2023); [5]Johnson et al. (2014); [6]Keen et al. (2016b).

cold acclimation of trout (Fig. 2, Table 2) causes cardiac hypertrophy as well as changes to contractile function and tissue composition (Klaiman et al., 2011, 2014; Keen et al., 2016a, 2017). This response is thought to be initiated by an increase in blood viscosity caused by an increase in the stiffness of the cell membranes of erythrocytes, which results from a decrease in physiological temperature (Graham and Farrell, 1989; Klaiman et al., 2011; Keen et al., 2016a). Such an increase in blood viscosity would increase vascular resistance as well as biomechanical strain on the heart. Cardiac remodeling caused by cold acclimation is reversible in zebrafish (*Danio rerio*) with rewarming (Shaftoe et al., 2023), and warm acclimation of trout causes a decrease in collagen content of the heart, an increase in the thickness of the compact myocardium (see Glossary) and a decrease in passive stiffness of the

Table 2. Summary of the impact of cold acclimation, warm acclimation and rewarming following cold acclimation on the structure and function of the hearts of rainbow trout (*Oncorhyncus mykiss*), zebrafish (*Danio rerio*) and red-eared slider turtle (*Trachemys scripta*)

	Rainbow trout		Zebrafish		Red-eared slider turtle
	Warm acclimation	Cold acclimation	Cold acclimation	Rewarmed following cold acclimation	Cold acclimation
Size of ventricle	≅[1,2]	↑[1,2]	↓[4]	↑[4]	↑[7]
Compact layer thickness	↑[1,2]	↓[1,2]	↓[4]	↑[4]	
Collagen content	↓[1,2]	↑[1,2]	↓[4,5]	↑[4]	↑[7]
Heart rate	↑[7,8,9]	↑[10]	≅[4,6]	≅[4]	
Averaged developed pressure	↓[2,3,4]	↑[2,3]			
Cardiac output			≅[4]	↑[4]	
Contraction force	=[2,3,4]	↑[3]			↑[7]
Stiffness	↓[1,2]	↑[2]			

[1]Klaiman et al. (2011); [2]Keen et al. (2016a); [3]Klaiman et al. (2014); [4]Shaftoe et al. (2023); [5]Johnson et al. (2014); [6]Little and Seebacher (2014a,b); [7]Keen et al. (2016b); [8]Keen et al. (1994); [9]Graham and Farrell (1989); [10]Aho and Vornanen (2001).

myocardium (Klaiman et al., 2011, 2014; Keen et al., 2016a) (Fig. 2, Table 2). LV and RV hypertrophy also occur in lowland deer mice (*Peromyscus leucopus*) with hypoxia exposure at sea level (Velotta et al., 2018). For the RV, this is thought to be in response to an increase in hematocrit, whereas LV hypertrophy is thought to result from an increase in contractile activity, both of which occur in response to hypoxic conditions (Velotta et al., 2018). Although changes in hemodynamic load caused by thermal acclimation and hypoxia exposure can result in cardiac hypertrophy, other comparative models have demonstrated that such a stimulus is not needed. For example, cardiac hypertrophy is observed in red knots (*Calidris canutus*) prior to migration (Morrison, 2006; Piersma et al., 1999) and in Burmese pythons (*Python molurus*) following a meal after a fast (Andersen et al., 2005). However, the hypertrophic response observed in pythons is not consistent, and recent work suggests that it requires a decrease in hematocrit (Slay et al., 2014; Jensen and Wang, 2024). Studies of the lungfish (*Protopterus dolloi*) demonstrate that aestivation causes an increase in cellular necrosis within the myocardium but that this disappears following arousal (Icardo et al., 2008). These examples show that the vertebrate heart can be plastic, enabling adjustments as metabolic requirements change.

Just as an increase in hemodynamic load causes morphological changes, it also initiates changes to myocyte contractility that contribute to changes in organ function. For example, cardiac myocytes from mammalian hearts exhibiting physiological cardiac hypertrophy show enhanced Ca^{2+}-handling properties (Gwathmey et al., 1991; Carvalho et al., 2006). These changes include increased sarcoplasmic reticulum (SR) Ca^{2+} release during activation, increased SR Ca^{2+} content and greater sensitivity to isoproterenol, a β-adrenergic receptor agonist. Conversely, there can be dysregulation of Ca^{2+} handling in hearts exhibiting pathological hypertrophy (Feldman et al., 1987; Gwathmey et al., 1987; Ke et al., 2020). These functional consequences are due, at least in part, to changes in the function and/or expression of SERCA2a and RyR2 (de la Bastie et al., 1990; Arai et al., 1996). In mammalian models, exercise training increases the Ca^{2+} sensitivity of force generation by the myocardium (Diffee et al., 2001). Cold acclimation of trout also increases Ca^{2+} sensitivity (Klaiman et al., 2014), SERCA activity (Aho and Vornanen, 1998), and the rate and level of pressure generation (Klaiman et al., 2014). These changes are thought to compensate for the influence of a decrease in temperature on myofilament function, and are caused, at least in part, by changes in the phosphorylation and expression of the contractile proteins (Alderman et al., 2012). Please see Keen et al. (2017) for further discussion of the remodeling response of the fish heart with thermal acclimation.

Overview of activation of the renin–angiotensin system

One signaling pathway involved in mechanosensitive cardiac remodeling is the renin–angiotensin system (see Bhullar and Dhalla, 2022 for in-depth review). The renin–angiotensin system is a modifier of cardiovascular performance that influences multiple points along the signaling cascade that regulate cardiac morphology and function in vertebrates. The peptides renin and angiotensin (ANG) are expressed in all extant vertebrate lineages, and specialized ANG-type (AT) receptors are found in most vertebrates (Nishimura, 2001). Renin is secreted by the kidneys in response to β-adrenergic stimulation, nitric oxide (NO) or a decrease in blood pressure (Kurtz, 2012). Negative regulators of renin secretion include high blood pressure, hypercalcemia and ANG II (Kurtz, 2012) (Fig. 3). Renin cleaves the angiotensin precursor, angiotensinogen, to produce ANG I, which is subsequently cleaved to ANG II by ANG-converting enzyme (ACE) (Oro et al., 2007). AT receptors (AT_{1a}, AT_{1b} and AT_2) are pivotal components of tissue-specific renin–angiotensin system signaling (see Fig. 4 for more information on ANG II signaling in the heart). For example, ANG II can stimulate cardiac remodeling directly by binding to AT_1

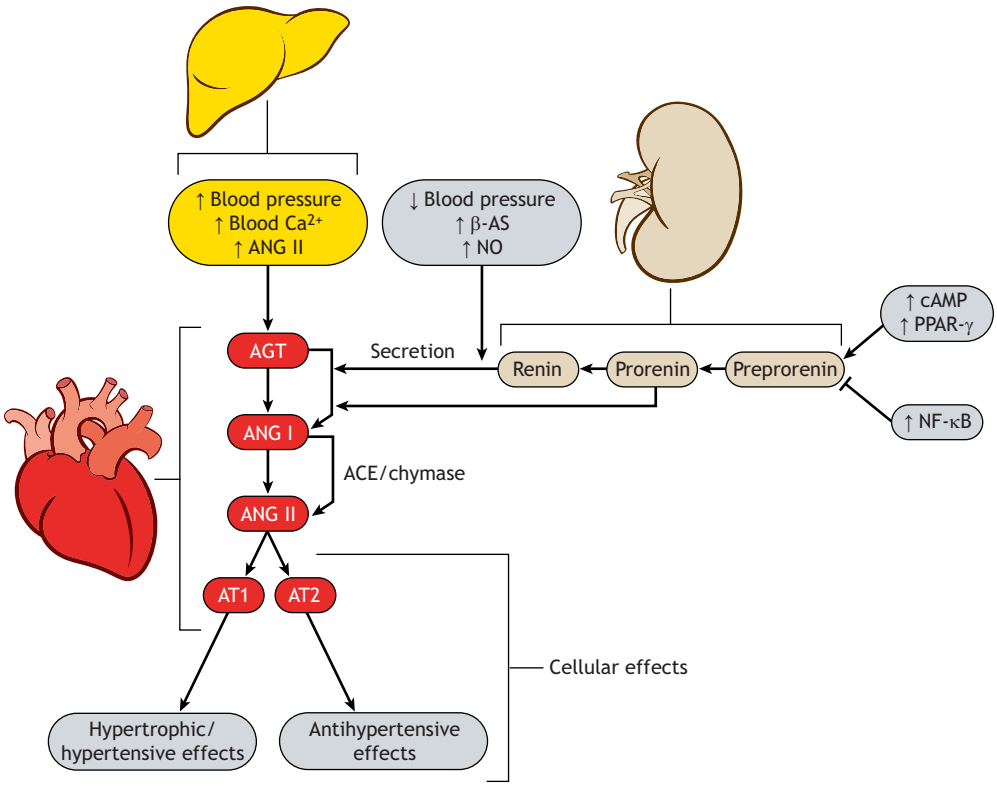

Fig. 3. Factors influencing renin secretion, transport and downstream activation of angiotensin receptors at cardiac tissue. Renin is expressed in the granular juxtaglomerular cells of the kidney from peptide precursors in response to neurohormonal stimulus. It is then secreted to the blood and transported to the liver, where renin catalyzes the conversion of angiotensinogen to angiotensin I, which is converted to angiotensin II by angiotensin-converting enzyme or chymase. Angiotensin II binds to membrane-specific receptors at target tissues which mediate signals that influence cardiac structure and function. The colours red, yellow and beige indicate the organ systems in which the listed responses or cellular components and pathways are located. Red, heart; yellow, liver; beige, kidney. Grey indicates pathways, components and consequences that are external to the three organs listed above.

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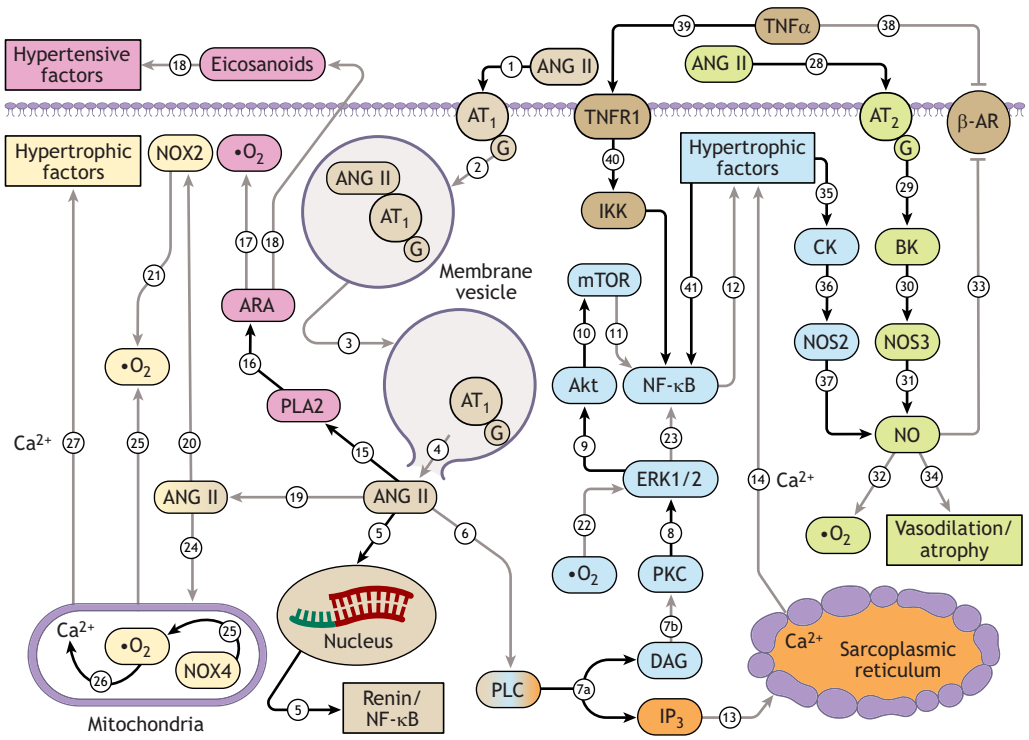

Fig. 4. Model of cellular interactions initiated by angiotensin II in the heart. Components of the signaling pathways are indicated by colored shapes with the abbreviated names as labels. Arrows connecting cellular components indicate an interaction between them. Black arrows indicate an enzymatic interaction. Gray arrows represent a translocation, non-enzymatic interaction or a condensed summary of a consequence. Numbers correspond to Table 3, where the processes involved in each interaction are summarized. In this figure beige indicates the canonical signaling pathway of translocated ANG II as a transcription factor. Pink indicates the effects of ANG II mediated by phospholipase 2. Yellow shows the influence that ANG II has on intracellular reactive oxygen species ($•O_2$) and Ca^{2+} via NADPH oxidase 2/4. Blue and orange show the activation of hypertrophic signals by ANG II via phospholipase C: blue is the Akt–mTOR–NF-κβ cascade and its downstream feedback via nitric oxide production; orange shows changes in sarcoplasmic Ca^{2+} release. Green shows vasodilatory signaling of ANG II bound to AT_2 receptors via nitric oxide. Brown shows how tumor necrosis factor α interacts with ANG II signaling. Abbreviations are defined in the List of symbols and abbreviations.

in the heart (De Gasparo et al., 1994) (Fig. 4, Table 3). In murine renal and cardiac tissues, AT_1 receptors are G-protein coupled, whereas AT_2 are not (Bottari et al., 1991; Bhullar and Dhalla, 2022). Activation of AT_1 receptors leads to 'adaptive remodeling' through the ERK1/2 pathway in the mammalian heart (Bhullar and Dhalla, 2022), and *in vitro* work demonstrates that the effects of ANG II on cardiac structure are stretch-inducible (Sadoshima et al., 1993).

When the renin–angiotensin system is overstimulated, adaptive remodeling (which includes cardiac hypertrophy) can become pathological (Bhullar and Dhalla, 2022). For example, occlusion of the carotid artery in dogs increases the pressure threshold that inhibits renin secretion, leading to constitutively elevated blood pressure (Kirchheim et al., 1985). This mimics the pressure overload seen in concentric hypertrophy models. It is thought that the prolonged activation of AT_1 contributes to the transition from adaptive to pathological remodeling (Bhullar and Dhalla, 2022). When ANG II binds to AT_1 receptors, multiple signaling cascades are initiated that lead to cardiac hypertrophy and cardiovascular hypertension; this signaling is mediated in part by ROS production (Fig. 4). At low concentrations, ROS are adaptive, but an imbalance in redox state is thought to cause maladaptive remodeling (Bhullar and Dhalla, 2022). Specifically, overstimulation of Akt–mTOR–NF-κB signaling is caused by ROS, phospholipase C (PLC) and tumor necrosis factor (TNF), the levels of which are elevated by ANG II signaling at AT_1 receptors (Bhullar and Dhalla, 2022; Khan et al., 2015; Sriramula and Francis, 2015).

The activation of AT_2 is less well understood than that of AT_1, but it appears to serve as a negative feedback that opposes the maladaptive actions of ANG II through AT_1 (Nehme et al., 2019). The pathway by which AT_2 affects cardiac structure is not clearly understood (Oro et al., 2007); however, we know that activation of the AT_2 membrane receptor stimulates the release of bradykinin from kininogen, increasing NO production and leading to vasodilation (Lemarie and Schiffrin, 2010) (Fig. 4, Table 3). Several derivatives of angiotensinogen are involved in mediating the downstream effects of AT_1 and AT_2 signaling in mammalian systems (Nehme et al., 2019). In the eel (*Anguilla japonica*), exogenous ANG II causes an increase in AT_2 abundance that is associated with cardiac growth and the maintenance of stroke volume after pressure overload (Imbrogno et al., 2013). This sort of cardiac growth, without a decrease in ventricular volume, mimics eccentric physiological remodeling. It should be noted, however, that Imbrogno et al. (2013) did not measure changes in AT_1 abundance, so the role of AT_1 in cardiac remodeling induced by exogenous ANG II in the eel is not known. Other angiotensinogen-derived peptides (i.e. ANG III, IV) are expressed in eel cells but their roles in the heart are unknown (Wong and Takei, 2013). Finally, we note that both ANG I-7 (which binds to Mas membrane receptors, and is another derivative peptide of angiotensinogen) and ANG IV (which binds to a specific AT_4 receptor) can attenuate the pathological cardiac hypertrophic response induced by Ang II (Bhullar and Dhalla, 2022; Park et al., 2016). The role of these secondary derivatives of angiotensinogen in non-mammalian

Table 3. Summary of cellular interactions in response to angiotensin II signaling

Label	Major component	Brief description	Source
1	ANG II	Binds AT_1 receptor in membrane	Bhullar and Dhalla (2022)
2	G-coupled AT_1 receptor	Internalization within membrane vesicle	Bhullar and Dhalla (2022); Lemarie and Schiffrin (2010)
3	Membrane vesicle	Translocates to nucleus	Bhullar and Dhalla (2022)
4	Membrane vesicle	Cleavage at nuclear membrane releasing ANGII into cytosol	Bhullar and Dhalla (2022)
5	ANG II, nuclear promotors	Nuclear binding factor to regulate renin secretion	Baker et al. (1992); Brasier et al. (2000); Eggena et al. (1993)
6	ANG II	Activation of PLC in cytosol	Bhullar and Dhalla (2022)
7	PLC	Catalyzes synthesis of DAG+IP_3	Bhullar and Dhalla (2022)
7b	DAG	Activates PKC	Lučić et al. (2016)
8	PKC	Phosphorylates ERK (activates)	Bhullar and Dhalla (2022)
9	ERK	Phosphorylates Akt	Bhullar and Dhalla (2022)
10	Akt	Phosphorylates mTOR	Dan et al. (2014)
11	mTOR	Activates NF-kB	Dan et al. (2008)
12	NF-κB	Upregulates hypertrophic/fibrotic factors*	Bhullar and Dhalla (2022)
13	IP_3, Ca^{2+} channels	Sarcoplasmic reticulum Ca^{2+} into cytosol	Bhullar and Dhalla (2022)
14	Ca^{2+}	Upregulates hypertrophic factors*	Bhullar and Dhalla (2022)
15	ANG II	Action unclear: activates PLA2	Khan et al. (2015)
16	PLA2	Upregulates arachidonic acid production from phospholipids	Khan et al. (2015)
17	Arachidonic acid	Increases ROS production (see label 22)	Khan et al. (2015)
18	Arachidonic acid, eicosanoids	Multiple downstream components for mediating pro-/anti-fibrotic factors*	Khan et al. (2015)
19	ANG II	Translocates through cell	Bhullar and Dhalla (2022)
20	ANG II	Activates NOX2	Bhullar and Dhalla (2022)
21	NOX2	Increases ROS production	Bhullar and Dhalla (2022)
22	ROS	Interacts with ERK1/2	Bhullar and Dhalla (2022)
23	ERK1/2, NF-κB	Upregulates hypertrophic/fibrotic factors*	Bhullar and Dhalla (2022)
24	ANG II	Translocates to mitochondria, activates NOX4	Bhullar and Dhalla (2022)
25	NOX4	Increases ROS production (see label 22)	Bhullar and Dhalla (2022)
26	ROS, Ca^{2+}	Stimulates release of mitochondrial Ca^{2+} into cytosol	Bhullar and Dhalla (2022)
27	Ca^{2+}	Upregulates hypertrophic factors*	Bhullar and Dhalla (2022)
28	ANG II	Binds AT_2 receptor in membrane	Lemarie and Schiffrin (2010)
29	AT_2 receptor	Stimulates BK production	Lemarie and Schiffrin (2010)
30	BK	Catalyzes NOS3	Lemarie and Schiffrin (2010)
31	NOS3	Increases NO production	Lemarie and Schiffrin (2010)
32	NO	Generates ROS (see label 22)	Tsutsui et al. (2011)
33	NO	Triggers systemic vasodilation and atrophy*	Lemarie and Schiffrin (2010)
34	NO, β-AR	Attenuates responsiveness of β-AR to activation*	Conti et al. (2013); Queen and Ferro (2006); Ungureanu-Longrois et al. (1995a,b)
35	Cytokines	Downstream targets of ERK signals to cardiomyocytes	Ungureanu-Longrois et al. (1995a,b)
36	Proinflammatory cytokines	Induce NOS2	Tsutsui et al. (2011)
37	NOS2	Increases NO production (see label 32)	Tsutsui et al. (2011)
38	TNFα, GRK2	Attenuates responsiveness of β-AR to activation*	Schumacher and Naga Prasad (2018)
39	TNFα, TNFR	TNFα binds TNFR	van Loo and Bertrand (2023)
40	TNFR, IKK	Stimulates E3 ubiquitin ligase (IKK) synthesis	van Loo and Bertrand (2023)
41	IKK, NF-κB	Phosphorylates inhibitor to NF-κB	Sun and Ley (2008)

Numbers correspond to Fig. 4, where the pathways involved in these interactions are mapped. Abbreviations are defined in the List of symbols and abbreviations.
*Descriptions representing a change in cardiac phenotype.

models is not fully understood. The differential activation of renin–angiotensin system components can lead to different cardiac responses, and work in comparative models reveals states that resemble both physiological and pathological remodeling seen in mammalian models. More research is needed to compare the renin–angiotensin system between mammals and non-mammalian models.

Changes in the relative abundance of different components of the renin–angiotensin system are important for controlling heart structure and function. For example, work in sheep shows that AT_2 is abundant during fetal development and decreases rapidly after birth, whereas AT_1 levels remain constant (Samyn et al., 1998). Both receptors are necessary for embryological cardiac development (Samyn et al., 1998). The effects of AT_2 stimulation appear to counteract those of AT_1 stimulation, such that inhibiting AT_2 receptors increases the hypertrophic response (Van Kesteren et al., 1997). Thus, the decrease in AT_2 abundance through ontogeny could lead to increased risk of pathological remodeling. This idea is supported by work on American eels, in which elevated expression of mRNA transcripts for the AT_2 receptor are seen after 8 weeks of exposure to ANG II, which causes increases in the thickness of compact myocardium, endothelial density, collagen deposition and cardiac hypertrophy (Filice et al., 2017), indicative of pathological remodeling. This is also associated with a decrease in the production of NO (Filice et al., 2017). In zebrafish, exposure to exogenous ANG II leads to ventricular hypertrophy, increased collagen deposition, upregulation of AT_1 and AT_2 receptors and increased heart rate (Filice et al., 2021a). As changes in AT_1

receptor density were not measured in the eel study, it is not known whether their response to exogenous ANG II differs from that of zebrafish in this regard. Further work has suggested that a decrease in the abundance of ACE (which would lead to a decrease in ANG II) in the zebrafish heart after 1 week of cold exposure (Shaftoe et al., 2024) underlies the decrease in collagen abundance and thickness of the compact myocardium previously observed in cold-acclimated zebrafish (Johnson et al., 2014; Shaftoe et al., 2023). By contrast, 4 weeks of warm exposure increases renin abundance in the kidney of goldfish (Lacy and Rahman, 2022), which would enhance hypertrophic signaling. An increase in collagen deposition coupled with muscle hypertrophy would be characterized as pathological in mammalian systems, whereas these changes appear to compensate for environmental change in trout and zebrafish (Keen et al., 2017; Shaftoe et al., 2023). Thus, investigating the combined effects of physiological challenges, such as temperature change and exercise, on comparative models can help to reveal interactions such as changes in metabolic demand with increased aerobic requirements that are not apparent in a homeothermic system.

Potential role of the renin–angiotensin system during cold-induced cardiac remodeling in fish

The role of the renin–angiotensin system in cardiac remodeling, specifically hypertrophic growth and increased collagen deposition, suggests that it contributes to the hypertrophic and hypertensive response of some fish to a change in temperature. Cardiac remodeling in fishes is dynamic, based on the direction of a temperature change (Keen et al., 2016a, 2018, 2021), and in zebrafish, the changes are reversible (Shaftoe et al., 2023). Indeed, inhibiting ACE can prevent and reverse left ventricular dilation (Konstam et al., 2000; Reis Filho et al., 2015). Blocking β-adrenergic signals, which can result from AT_2 stimulation (Table 3), also has a significant positive effect on idiopathic dilation (i.e. that for which the cause is unknown; Hoshikawa et al., 2011). The role that the angiotensin system plays in the reversibility of cardiac remodeling in comparative models is not known. In addition, the response of the heart to a change in temperature is species dependent (Fig. 2, Table 2). For example, cold-acclimated rainbow trout and zebrafish both display a decrease in the thickness of the compact myocardial layer of the ventricle (Johnson et al., 2014; Keen et al., 2016a; Klaiman et al., 2011), but zebrafish show decreased collagen abundance in the ventricle (Johnson et al., 2014; Shaftoe et al., 2023), whereas ventricular collagen abundance increases in trout (Keen et al., 2016a; Klaiman et al., 2011) (Fig. 2, Table 2). Whether the renin–angiotensin system plays a role in these species-specific responses is not known.

The renin–angiotensin system in the activation of cytokine signaling

Work in rats indicates that AT receptors are sensitive to changes in temperature, and that they act to increase vascular resistance at low temperature (Sun et al., 2001, 2002). This supports a role for the renin–angiotensin system in initiating cold acclimation in vertebrates. Recent work in zebrafish suggests that a decrease in ACE abundance in the first week of cold exposure may be important for initiating subsequent remodeling responses (Shaftoe et al., 2024). As ANG II exposure causes cardiac hypertrophy and collagen deposition in zebrafish along with an increase in AT receptor abundance (Filice et al., 2021a; Joshi et al., 2021), the decrease in ACE abundance implicates the renin–angiotensin system in cold acclimation in teleost fish. It is thought that some of the activity of AT receptors is mediated through cytokine signaling. For example, activation of the AT_1 receptor in mice is correlated with increased activity of NF-κβ signaling (Bhullar and Dhalla, 2022) (Fig. 4, Table 3), and NF-κβ inhibition abrogates the ANG II-induced activation of transforming growth factor β (TGF-β) in rat lungs (Meng et al., 2014). TGF-β is a cytokine that mediates endothelial repair at the site of injury in the heart (Bujak and Frangogiannis, 2007). Addition of TGF-β to isolated trout cardiac fibroblasts increases collagen deposition, as seen in the ventricle of cold-acclimated trout (Johnston and Gillis, 2017). As mentioned above, MAPK phosphorylation is implicated in the stretch-inducible pathway for collagen deposition both in isolated fibroblasts (Johnston and Gillis, 2020) and also *in vivo* following cold acclimation (Ding et al., 2022). Therefore, understanding the interplay between these cellular pathways as well as cell-specific responses (i.e. fibroblasts versus myocytes) is essential to allow us to understand the development of physiological and pathological remodeling in the vertebrate heart.

It is interesting to note that the cardiac remodeling shown by a variety of fish species in response to environmental conditions exhibits characteristics indicative of pathological remodeling in mammals (Keen et al., 2017), but that this remodeling appears to improve the contractile properties of the heart (Klaiman et al., 2011, 2014). However, it should be noted that cold acclimation of trout also causes an increase in collagen deposition and hypertrophy of the myocardium, but there is little data characterizing the consequences of such changes on diastolic function. Future studies using cardiac ultrasound may provide further insight into the functional consequences of thermal acclimation. It is also important to consider context when deciding whether the net effect of a remodeling response is positive or negative. For example, in mammalian models, different types of exercise (aerobic versus resistance training) induce different patterns of adaptive remodeling, and these changes increase the capacity of the animal to complete the relevant activity (Arbab-Zadeh et al., 2014; Dinis et al., 2018; La Gerche et al., 2017). Further work is needed to clarify the role of cardiac remodeling in different contexts and to determine how cellular mechanotransduction (e.g. titin kinase) and the interaction between the renin–angiotensin system and cytokine signaling mediate the transition from physiological to pathological remodeling.

Overview of the NO system in remodeling

The role of NO as a signaling molecule in the cardiovascular system in vertebrates is well established (Locascio et al., 2023). Nitric oxide synthase (NOS) is a major source of NO in living cells and plays an important role in regulating cardiorespiratory function under adverse conditions (Filice et al., 2021b). There are three NOS genes in mammals that are expressed primarily in neural (nNOS), endothelial (eNOS) and macrophage (iNOS) cells in a variety of tissues, including the heart and kidneys (Locascio et al., 2023). Homologues of these three genes are found in representatives from all non-teleost chordates (Locascio et al., 2023). Although only two NOS genes have been identified in teleosts, there is evidence that gene duplicates have acquired the same function (Giordano et al., 2022). Recent work has highlighted the inadequate classification of NOS genes in vertebrates, and argues that mammalian nNOS, iNOS and eNOS be classified as NOS1, NOS2 and NOS3, respectively, to reflect the order of discovery (Locascio et al., 2023). We will use this nomenclature going forward.

NO is a vasodilator whose activity is partially regulated by bradykinin, a signaling peptide induced by AT_2 activation (Padia and Carey, 2013; Vaziri et al., 2005) (Fig. 4, Table 3). NO stimulates renin secretion through G-coupled increases in cyclic adenosine

monophosphate (Krop and Danser, 2008). Thus, NO activity is directly related to the activation of the renin–angiotensin system (Bekassy et al., 2022). NO, much like ANG, has a diverse range of physiological effects that depend on the cellular context of its synthesis. The interactions have been reviewed elsewhere (Strijdom et al., 2009); however, to compare physiological with pathological outcomes, we will summarize some of the major points. NO is cardioprotective (Prabhu, 2004) – producing anti-fibrotic effects and stimulation of cardiac output – when expressed at low dosages by NOS3 and NOS1. NOS3, which is localized in the caveolae of endocardial cells of mammals, inhibits L-type Ca^{2+} channels, reducing the force of cardiac contractions (Strijdom et al., 2009). NOS3 also appears to mediate the Frank–Starling response in isolated perfused hearts of goldfish by increasing NO, which increases stroke volume (Imbrogno et al., 2014). Work in trout demonstrates that NO decreases contraction rate and strength in a dose-dependent manner (Carnevale et al., 2021). NOS1, which is localized in the SR of mammalian cardiomyocytes, opens ryanodine receptors, increasing the force of cardiac contractions (Strijdom et al., 2009). Therefore, the interplay between NOS isoforms is likely to moderate NO production to regulate cardiac performance, similar to the roles of AT_1 and AT_2 in the renin system.

NOS2 is expressed in response to the release of stretch-inducible cytokines, such as tumor necrosis factor α (TNFα) or interleukin (IL) 2 (Finkel et al., 1992). NOS2 produces NO at a higher rate than that of NOS3 or NOS1; thus, it can lead to pathological remodeling (Strijdom et al., 2009). TNFα, at least, appears to have rapid effects on myocyte function and long-term effects mediated by NO (Ungureanu-Longrois et al., 1995a). NO produced by NOS2 can react with sulfur groups and form nitrosothiol, which may serve a cardioprotective role as a signaling molecule or alter redox state (Subhash Peter et al., 2022). In the presence of supraphysiological superoxide ($O_2^{\bullet-}$), NO forms peroxynitrite, with proinflammatory consequences (Ronson et al., 1999). Importantly, cardiac hypoxia causes an increase in NO production that may be independent of NOS3 activity (Strijdom et al., 2009). NO plays an important role in maintaining energy supply to metabolically demanding tissues during periods of hypoxia, through vasodilation and the upregulation of glycolysis (Almeida et al., 2004; see Umbrello et al., 2013). In teleosts, NO also conserves cardiac power output during prolonged exercise and enhances repolarization via K_{ATP} channels, which is required to maintain an increase in heart rate (Cameron et al., 2003; Carnevale et al., 2021). By contrast, its oxidative derivatives inhibit the mitochondrial electron transport chain (ETC), potentially sensitizing cells to hypoxia (Brown and Borutaite, 2007). There is evidence that the effects of NO on cardiac function are dependent on the presence of insulin and the cohort of available cytokines in the cytosol of cardiac microvascular endothelial cells (Ungureanu-Longrois et al., 1995b).

The low concentration of NO produced by NOS3 preserves Ca^{2+} cycling in ventricular myocytes and prevents cell death by inhibiting the formation of the mitochondrial permeability transition pore (see Glossary; Tastai et al., 2014; Sasaki et al., 2000). Interestingly, prolonged inhibition of NO synthesis by L-NAME, a non-specific inhibitor of NOS activity, increases the accumulation of ROS and subsequent collagen deposition, leading to renal and cardiac fibrosis in mammalian models (Ferrini et al., 2002). This indicates that NOS2 has both cardioprotective and pathological functions (uncoupling NO production from renin secretion). In salmonids, the effects of NO in hypoxia depend on the level of strain experienced by the myocardium (Carnevale et al., 2021). For example, the effect of the NO donor sodium nitroprusside on net power production by myocardial strips is greater at higher strain (Carnevale et al., 2021). NO production by NOS2 is important for maintaining cardiorespiratory function during hypoxia across vertebrate lineages (Subhash Peter et al., 2022). Therefore, fish represent a good model for cardiac remodeling that is mediated by NO, sensitive to myocardial strain, and interacts with the renin–angiotensin system. However, although NOS2 is implicated in improved prognosis following ischemic shock (Liu et al., 2005), relatively little is known about the consequences of NOS2 activation for fish cardiac structure (Subhash Peter et al., 2022). Thus, further research is required to reveal how the physiology of ectotherms prevents the development of cardiopathies, especially considering the prevalence of run-away signaling in the homeothermic context.

Role of ROS in cardiac remodeling

ROS are oxygen-containing molecules that are highly reactive and produced by multiple cellular processes. Specific ROS include hydrogen peroxide (H_2O_2), superoxide ($O_2^{\bullet-}$), hydroxyl radical ($OH^{\bullet}$) and singlet oxygen ($^1O_2$). In the heart, $O_2^{\bullet-}$ and H_2O_2 are produced by NADPH oxidase (NOX) and the mitochondrial ETC (Tsutsui et al., 2011), and the antioxidants superoxide dismutase, glutathione peroxidase and catalase are the primary regulators that keep ROS abundance within physiological parameters (Tsutsui et al., 2011). At low concentrations, ROS function as a cell signaling ligand, similar to NO. However, oxidative stress occurs when ROS production exceeds the capacity of antioxidant systems to remove ROS; at elevated concentrations, ROS react with membranes and proteins to cause significant cellular damage and, ultimately, Ca^{2+}-dependent cell death and organ dysfunction (Powers et al., 2020; Zuo et al., 2022). For example, excessive ROS production is implicated in the damage caused in mouse heart following ischemia–reperfusion (Szibor et al., 2020). Contrastingly, intermittent hypoxia of largemouth bass (*Micropterus salmoides*), which would cause increased ROS production during reoxygenation, promotes adaptation of the heart to hypoxia by increasing cardiac size, angiogenesis and NO production (Zhao et al., 2024). Pacific salmon (*Oncorhyncus gorbuscha*) on their terminal spawning migration also exhibit oxidative damage in the heart, suggesting a role of ROS production in the death of these fish (Wilson et al., 2014). As discussed briefly above, elevated concentrations of both ANG II and NO interact with ROS, increasing ROS accumulation at the mitochondria. However, ROS also serve a role in cardiac remodeling that is independent of these pathways. Experiments by Tsutsui et al. (2011) suggest that heart failure in mammals is closely associated with an increase in hydroxyls and therefore that the type/source of free radicals may play a role in disease progression.

The source of ROS in working muscles, including the heart, has been of significant interest. It is thought that ANG II-induced increases in phospholipase 2 (PLA2) activity would be one major pathway leading to ROS production (Powers et al., 2020) (Fig. 4, Table 3). An increase in PLA2 activity would lead to oxidation of membrane lipids and the production of eicosanoids (Khan et al., 2015), a form of oxidized fatty acid, some of which are elevated in hypertensive models (Nasjletti, 1998) (Fig. 4, Table 3). Another pathway for ROS production is through NOX2, which requires activation by a ligand such as ANG II (Powers et al., 2020) (Fig. 4, Table 3). Interestingly, elevated ROS production during exercise is important for stimulating adaptive remodeling in skeletal muscle (Powers et al., 2020), including through increases in NF-κβ and peroxisome proliferator-activated receptor-γ coactivator-1 protein α (PGC-1α) (Powers et al., 2010), both of which are significant contributors to the adaptive increases in antioxidants and

mitochondrial density observed after exercise (Powers et al., 2020). This complicates the discussion of whether ROS is harmful at high concentrations.

Signaling cascades that drive physiological remodeling toward pathological remodeling

Thyroid hormones appear to play a role in regulating the cardiac remodeling response; for example, they are thought to control the remodeling of the zebrafish heart to cold acclimation (Little and Seebacher, 2014b). However, the level of expression of the hormones is important. Endothermic species have higher concentrations of circulating thyroid hormones than ectothermic species (Little and Seebacher, 2014a), and this is thought to limit the capacity of endothermic species to heal cardiac tissue following damage (Ross et al., 2022). Thyroid hormone promotes renin secretion through its activation of β-adrenergic signaling (Ganong, 1982). Thus, hyperthyroidism can result in excessive renin release, contributing to hypertensive symptoms (Deschepper, 1994). The comparatively high thyroid hormone levels in homeotherms may predispose them to dysregulation of blood pressure.

In mammals, aldosterone is a major downstream mediator of renin-induced ANG activity, being implicated in several pathological conditions, such as heart failure, hypertension and insulin resistance (Nehme et al., 2019). Aldosterone acts through mineralocorticoid receptors, the same receptors that are activated by cortisol (Funder, 2017). Cortisol can contribute to pathology following ischemia–reperfusion injury through its effects on 11β-hydroxysteroid dehydrogenase type 1 (Funder, 2017). Fish that are chronically treated with cortisol develop pathological cardiac structure, and it is possible that the signaling pathway involves mineralocorticoid receptors and 11β-hydroxysteroid dehydrogenase (Johansen et al., 2017). Furthermore, a change in systemic resistance, for example, owing to exercise, leads to secretion of thyroid hormone via noradrenaline-induced secretion of thyrotrophin-releasing hormone (Hackney and Saeidi, 2019), which leads to renin secretion (Vargas et al., 2012). The chronic activation of this pathway could lead to the desensitization of the heart to β-adrenergic signals, a feature commonly associated with cardiac dysfunction (Sucharov et al., 2011).

There is significant interest in the cellular signals responsible for the transition from physiological to pathological cardiac remodeling, a process that occurs primarily in hearts that lack regenerative capacity. An effective model of this transition is the progression of cardiac growth in some athletes in response to aerobic exercise. This involves pathological remodeling of the RV in response to an exercise-induced increase in hemodynamic load, leading to dilation of the ventricle and systolic dysfunction (La Gerche et al., 2017). It has been proposed that athletes whose training regime does not balance activity with rest are prone to developing such cardiac dysfunction (La Gerche et al., 2017); it is possible that an increase in the frequency and consistency of a stressor without sufficient time to recover leads to dysregulation of the renin–angiotensin system, and the NOS and ROS signaling pathways. For example, extended periods of elevated blood pressure cause sensitization of renal pressure sensors, and this increases the pressure threshold that elicits renin release, leading to a phenotype in which hypertensive factors are cyclically stimulated. Repeated exercise also increases the production of ROS (which can lead to oxidative damage) and the release of pro-inflammatory cytokines when oxidative stress exceeds the capacity of the cell to control ROS levels. NOS2 is activated by an increase in pro-inflammatory cytokines, and the resulting excessive production of NO can lead to cardiac dysfunction (see Ungureanu-Longrois et al., 1995a). As discussed above, cytokines are important signaling proteins that are released in response to changes in cardiovascular load and tissue strain. ANG II secretion and β-adrenergic stimulation cause TNFα production by cardiac monocytes, leading to transcription of inflammatory cytokines (Ruiz-Ortega et al., 2002; De Angelis et al., 2019). In fact, TNFα may be required to mediate cardiac remodeling following the binding of ANG II to membrane receptors (Sriramula et al., 2015). One inflammatory pathway is through NF-κβ signaling, which itself induces the expression of TNFα, IL-1 and IL-6 (Schumacher and Naga Prasad, 2018). TNFα increases the expression of G-coupled receptor kinase 2 (GRK2), which phosphorylates β-adrenergic receptors, thus decreasing their sensitivity to sympathetic innervation (Vasudevan et al., 2013). This is not to say that the exercise stressor is the primary cause of heart disease in affected individuals; as mentioned above, the quality and quantity of rest following an exercise stressor is also relevant. This may be important in aquaculture, in which managing the frequency of a stressor may protect fish from pathological remodeling (Frisk et al., 2020).

It is important to consider the impact of multiple stressors when evaluating the changes to the heart during the transition from a physiological to a pathological state. Downstream mediators of cytokine signaling include the Akt/mTOR pathway (Vergadi et al., 2017), one of the pathways that is also activated by AT_1 stimulation (Fig. 4, Table 3). Rat cardiomyocyte slices exposed to simulated pressure overload increase markers of cytokine signaling, whereas simulated volume overload increases markers of Akt signaling (Pitoulis et al., 2022). These results demonstrate the significance of combined stressors in the development of pathology. For example, CMS is associated with increases in pulmonary arterial pressure, pulmonary vascular resistance and blood hemoglobin content, creating simultaneous pressure and volume overload (Doutreleau et al., 2022). This suggests that cytokine release and stimulation of the renin–angiotensin system may play a combined role in the development of CMS. In their recent review, Mares and Gupta (2022) highlight that the population at high altitude with the lowest incidence of CMS are the Tibetans, who, despite increased cardiovascular performance at altitude, do not exhibit elevated resting blood pressure or high hematocrit. This would suggest that some populations have a greater ability to adapt to adverse environmental conditions, just as differences in plasticity exist between natural populations. For example, subpopulations of redside dace (*Clinostomus elongatus*) differ in their thermal tolerance (Turko et al., 2021). Differences in plasticity between populations and subpopulations are relevant when considering both biomedical approaches to disease and conservation approaches to habitat change.

The value of comparative models in addressing questions of pathology

The adult mammalian heart is particularly vulnerable to damage because of the poor proliferative capacity of cardiomyocytes (González-Rosa et al., 2018). This is a trait shared by birds, leading researchers to hypothesize that homeothermy plays a role in explaining why the vertebrate heart is so vulnerable under certain circumstances (Shiels, 2022). Homeotherms require a lot of oxygen to meet the metabolic demands of tissues; they thus need a high cardiac output to deliver that oxygen through the blood. Interestingly, levels of ROS are elevated during the oxygen debt that occurs after anaerobic exercise; however, the cardiac response to regular burst exercise is that of increased function, not of

dysfunction (D'Ascenzi et al., 2018). Therefore, adaptive cardiac remodeling appears to be the result of a robust capacity to restore cellular homeostasis after a disturbance rather than a capacity to prevent the disturbance per se. This is where model organisms become very informative. Many animals live in highly variable environments where physiological disturbance occurs on different time scales; the physiological state of these animals changes concordantly. Such is the case for cold-acclimated ectotherms. Outside of behavioral adaptations, humans are limited to a fairly narrow physiological temperature range, whereas eurythermal fish, such as rainbow trout, can inhabit waters that vary more than 10°C annually with no more than physiological changes (Keen et al., 2017; Klaiman et al., 2011; Spence et al., 2006, 2008). Likewise, hypoxia-tolerant fish, such as crucian carp (*Carassius carassius*) or Pacific hagfish (*Eptatretus stoutii*), can remain active in water with little to no oxygen for months (carp; Johansen et al., 2023; Van den Thillart et al., 1983) or in hypoxic deep water, with short stints in anoxia (hagfish; Cox et al., 2011; Hansen and Sidell, 1983). These types of comparative models allow researchers to isolate adaptive mechanisms that protect non-human animals from cardiac injury under conditions that would kill many mammalian species. Therefore, a number of different model organisms should be utilized when studying cardiac remodeling, a phenomenon that has potential application in improving heart health in humans.

Conditions for pathological remodeling in comparative models

As discussed above, chronic or repeated exposure to increased hemodynamic load can drive pathological remodeling of the mammalian heart; this includes the development of RV hypertrophy in lowland deer mice with chronic hypoxia exposure (Velotta et al., 2018). However, there are no known studies that have demonstrated that a chronic hemodynamic stress can initiate pathological changes in a fish heart that result in a decrease in contractile function. For example, there is no change in the relative heart mass in trout that were chronically exercised for 2 weeks (Dindia et al., 2017), and although cold acclimation does cause an increase in collagen deposition in the trout heart, the rate and level of cardiac contraction in the intact heart is increased under these conditions (Klaiman, 2011, 2014). Conversely, work by Johansen et al. (2017) demonstrates that exposure of trout to increased levels of exogenous cortisol for 45 days leads to a pathological phenotype, including an increase in relative heart size and a decrease in cardiac output. However, in this experiment there was no difference in hematocrit between treatment and control fish, and it was proposed that the hypertrophy was caused by stress-induced, pro-hypertrophic signaling through nuclear factor of activated T-cell (NFAT) (Johansen et al., 2017).

Although it may be difficult to induce a pathological cardiac phenotype in fish using normal physiological challenges such as thermal acclimation or chronic exercise, concurrent changes in multiple environmental conditions caused by climate change may be of concern. For example, environmental temperatures are becoming more stochastic, and aquatic hypoxia is becoming common in freshwater systems (Bijma et al., 2013; Thorstad et al., 2021). This is relevant for anadromous salmon species, that complete athletically challenging migrations to natal streams through waters that are becoming increasingly warm and hypoxic (Patterson et al., 2007; Martins et al., 2011; Muir et al., 2022). Local hypoxic zones are also of concern; these are becoming more common as water levels decrease in years with reduced flow or owing to human-made obstructions (Gordon et al., 2015; Sergeant et al., 2017). These exposures are typically discrete stressors, but the cumulative impacts of multiple challenges – potentially coupled with stress-induced elevated levels of cortisol – may cause a pathological cardiac phenotype to become evident in these fish. Previous work has demonstrated that the cortisol response in Atlantic salmon is more pronounced as temperature increases (Madaro et al., 2018), and cortisol is a causative factor in the activation of ANG II through mineralocorticoid receptors at the kidneys (Sztechman et al., 2018). The consequence of the interaction between cortisol and the renin–angiotensin system is poorly studied in fish but warrants further attention in the context of environmental change. There is also evidence of cardiac remodeling that occurs in aquaculture. Farmed Atlantic salmon exposed to elevated temperature display a 20% increase in ventricular mass and, when paired with hypoxia, the fish exhibit reduced growth (Gamperl et al., 2020). The fast growth protocols that are used in aquaculture can lead to pathological remodeling in juvenile Atlantic salmon, including ventricular hypertrophy with no increase in chamber volume, and asymmetrical hypertrophy of the compact myocardium (Frisk et al., 2020). Investigating the development of domestic-strain pathology and a wild-type pathological heart is of importance to understanding the consequences of climate change on migratory salmon.

Conclusions and perspective

The ability of the vertebrate heart to remodel enables cardiac function to adapt to changes in physiological conditions or aerobic requirements. For example, this capacity enables some ectothermic species to maintain heart function at low environmental temperatures and allows pregnant mammals to better support a growing fetus. However, the same pathways that underlie remodeling also appear to make mammalian species susceptible to the development of pathological phenotypes when the cardiovascular system is exposed to increased aerobic demands with limited time for recovery. One potential reason for this is that mammalian cells function under narrow physiological parameters (e.g. temperature, dissolved O_2), but have relatively high energetic requirements. Such conditions increase the likelihood of cellular conditions that could lead to the activation of pathological pathways, including increases in intracellular ROS concentrations. Just as pathological remodeling occurs when the capacity of the heart to repair or prevent cellular damage is exceeded, so does pathology develop when the capacity of the cardiovascular system to meet metabolic demands is exceeded. These observations point to the adaptability of low-demand systems; for example, ectotherms can depress metabolic demand to reduce the impact of decreased cardiac function during remodeling. However, with natural populations exposed to environmental stressors that are increasing in both magnitude and number, there may be the potential for the development of pathological cardiac phenotypes if the capacity of the heart to regulate the physiological remodeling response is exceeded. Going forward, further study of species that maintain heart function despite exposure to combined stressors that push them to the limit of their capacity will be essential to understanding both human pathology and the risks to natural populations from changing environmental conditions.

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